REMARKS

The title of the specification has been amended as the Examiner requested.

Claims 1-7 have been amended and claims 29-34 have been added. These amendments are supported throughout the application as filed, e.g., at page 6, lines 9-23; page 26, lines 16-27; and Figures 1 and 3 and their accompanying description.

Claims 8-26 have been canceled as being drawn to non-elected inventions. As permitted under rejoinder practice, once the present claims are deemed allowable, Applicants intend to rejoin claim 27 (a method of making a polypeptide) and add other similar claims of a scope identical to the allowable polypeptide claims.

No new matter has been added.

Rejections Under 35 U.S.C. 112, First Paragraph

Written Description

Claims 1-4 and 6-7 are rejected as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that that the inventor(s), at the time the application was filed, had possession of the claimed invention." The Examiner contends that:

> The written description in this case only sets forth SEQ ID NO:1 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to variants of a polypeptide of SEQ ID NO:1, such variants being at least 70% identical, at least 80% identical, at least 95% identical and having up to 30 conservative substitutions in SEQ ID NO:2. (...) This is insufficient to support the generic claims as provided by the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday, January 5, 2001.
>
> Therefore, only an isolated polypeptide comprising the sequence of SEQ ID NO:1, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. As a result, it does not appear that the inventors were in possession of variants of a polypeptide of amino acid sequence set forth in SEQ ID NO:1. (See office action, pages 4-5.)

This rejection has been met, in part, by amending claim 1 to increase the required percent identity to 76%. The rejection is respectfully traversed with regard to the pending claims. The pending claims fully satisfy the written description requirement under Federal Circuit law and the Patent Office's own Written Description Guidelines (the Guidelines), which are cited by the Examiner. The Guidelines state that the written description requirement can be satisfied by:

> sufficient description of a representative number of species by actual reduction to practice. . . .or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (Federal Register, Vol. 66, No. 4, at page 1104).

Claims 1-4 and 6-7 clearly meet this standard, as do new claims 29-34, which are even more narrowly drawn. The claimed polypeptides are limited structurally in that they have a high degree of identity with SEQ ID NO:1, or are encoded by a nucleic acid that hybridizes under high stringency conditions to a specific sequence. They are also limited functionally in that they must have cation transporter activity. In addition, the specification provides ample guidance on the structural basis for cation transporter activity. As disclosed, e.g., at page 26, lines 16-27; and by Figure 1, cation transporter activity correlates with a hydrophobicity profile indicative of multiple transmembrane domains, with the presence of a GTP/ATP binding site, and with the presence of a transporter consensus sequence. Furthermore, contrary to the Examiner's statement, the specification discloses two representative examples of the claimed polypeptides, OCTN1 (SEQ ID NO:1) and OCTN2 (SEQ ID NO:3), which are 76% identical (See Figure 3 and its corresponding description and discussion in the specification).

With regard to claim 7 in particular, the Examiner is directed to Example 9 of the Synopsis of Application of Written Description Guidelines (the Synopsis of Application), which indicates that claims very similar to claim 7 are adequately described. The Examiner is reminded that the Federal Circuit, in *Enzo Biochem, Inc. v. Gen-Probe Inc.* (296 F.3d 1316, Fed. Cir. 2002), has taken judicial notice of the Guidelines and the Synopsis of Application. Referring to Example 9 of the Synopsis of Application, the Court stated "[the PTO] has determined that such claims may be adequately described if they hybridize under highly stringent conditions to known

sequences because such conditions dictate that all species within the genus will be structurally similar" (*Enzo*,296 F.3d 1316 at 1327).

Thus, the specification provides ample disclosure of specific, common structural features, as well as functional features, that serve to distinguish the claimed polypeptides within the claims from those outside the claims. Accordingly, one of ordinary skill in the art would understand that Applicants were in possession of the full scope of the claims.

Enablement

Claims 1-4, 6 and 7 are rejected as allegedly not enabled. The Examiner asserts that the claims are overly broad in their % identity and hybridization limitations and states that "no guidance is provided as to which of the myriad of polynucleotide species encompassed by the claims will encode a polypeptide which retains the characteristics of a transporter of an organic cation." In support of these arguments, the Examiner cites two articles that show that, for MIF and β-hemoglobin proteins, a single amino acid change affects structure and function.

This rejection is respectfully traversed with regard to the present claims. Applicants have provided two working examples of the claimed polypeptides (SEQ ID NO:1 and SEQ ID NO:3), that have cation transporter activity as claimed. The specification, e.g., Figure 3, provides guidance as to what regions of the polypeptides are conserved or divergent. An ordinary artisan could use this information, coupled with the knowledge in the art, to determine what regions of the polypeptides can tolerate changes while still retaining transporter activity. For example, an ordinary artisan would predict that the transporter consensus sequence is important for transporter function (see, e.g., page 6, lines 15-23). In addition, Applicants provide detailed description of transporter assays that can be used to determine whether a particular polypeptide has activity (see, e.g., Examples 6-8).

Applicants fail to see how the MIF and β-hemoglobin references cited by the Examiner provide evidence that the presently claimed polypeptides are not enabled. The enablement requirement is satisfied if an ordinary artisan could make and use the claimed polypeptides. As discussed above, using merely routine experimentation, one could make the polypeptides having the required structures and test them for cation transporter activity. Polypeptides that do not have transporter activity would simply not be covered by the present claims. Furthermore,

Applicants have identified two polypeptides, OCTN1 (SEQ ID NO:1) and OCTN2 (SEQ ID NO:3), that differ in sequence but do have the required functional activity. While it is surely true that in some instances a single amino acid substitution can affect the function of a polypeptide, it also recognized in the art that, for any given protein, many residues can be substituted without affecting a specified function. This much is exemplified by Applicants' own disclosure of SEQ ID NO:1 and 3, and by the prior art. See, e.g., Bowie et al. (1990) *Science* 247:1306-1310 (copy enclosed). At page 1306, lines 12-13, Bowie teaches that "proteins are surprisingly tolerant of amino acid substitutions". Bowie et al. cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (Bowie at page 1306, col. 2, lines 14-17). Presumably the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on Bowie et al.'s teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity. These are far better odds than those at issue in *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), in which the court said that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question is not whether it is possible to abolish activity with a point mutation (as the Examiner seems to believe), but rather whether one of ordinary skill can produce, without undue experimentation, mutants in which the activity is not abolished. Based on Bowie et al.'s teachings, one would predict that even random substitution of residues in SEQ ID NO:1 will predictably result in a majority of the variants having full or partial transporter activity.

In sum, the fact that it may be theoretically possible to make a variant that lacks function seems irrelevant to the question of whether one of ordinary skill in the art would know how to make and use variants of the claimed polypeptides that retain function without undue experimentation. The Examiner has provided no evidence that one of ordinary skill could not use the guidance provided in the specification (e.g., the alignment shown in Figure 3, showing conserved and divergent regions of OCTN1 and 2) to predict and determine (by routine testing) what amino acids could be changed without affecting cation transporter function. Given the specific limitations recited in the claims, the high level of skill in the art, the detailed guidance

provided by Applicants, the disclosure of two working examples, and the routine nature of any experimentation that might be required to make and use the claimed polypeptides, the present claims are clearly enabled.

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 1-7 are rejected as indefinite.

Claim 7 is said to be indefinite in the recitation of the phrase "hybridizes under stringent conditions." This rejection has been met by amending the claim to recite specific conditions of high stringency, as disclosed at page 12, lines 6-14, of the specification. Claims 1-7 are said to be indefinite for reciting non-elected sequences. This rejection has been met by amending the claims to delete references to SEQ ID NOs:3, 22 and 27. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. 102(e)

Claim 7 is rejected as allegedly anticipated by U.S. Patent No. 6,063,623 to Koepsell (Koepsell). The Examiner indicates that Koepsell discloses "a transport protein (see abstract) with 33.7% identity in about a 540 amino acid overlap with SEQ ID NO:1." The Examiner believes that DNA encoding the Koepsell protean would hybridize under stringent conditions to SEQ ID NO:2.

The rejection has been met by amending claim 7 to recite specific hybridization conditions of high stringency. In light of the very low degree of homology between Koepsell's DNA and the DNA of SEQ ID NO: 2, the two would not hybridize under the hybridzation conditions presently recited in claim 7. Accordingly, the rejection has been overcome.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 11 December 2002

Leda Tsirimo, Reg. No. 50,635
for: Janis K. Fraser
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

Version with markings to show changes made

In the claims:

Claims 1-7 have been amended as follows:

1. (Amended) A substantially pure polypeptide comprising an amino acid sequence at least [70%] 76% identical to [any one of SEQ ID NOs:1, 3, 22, or 27] SEQ ID NO:1, wherein the polypeptide is a transporter of an organic cation.

2. (Amended) The polypeptide of claim 1, wherein the amino acid sequence is at least 80% identical to [any one of SEQ ID NOs:1, 3, 22, or 27] SEQ ID NO:1.

3. (Amended) The polypeptide of claim 1, wherein the amino acid sequence is at least 90% identical to [any one of SEQ ID NOs:1, 3, 22, or 27] SEQ ID NO:1.

4. (Amended) The polypeptide of claim 1, wherein the amino acid sequence is at least 95% identical to [any one of SEQ ID NOs:1, 3, 22, or 27] SEQ ID NO:1.

5. (Amended) A substantially pure polypeptide comprising the sequence of [any one of SEQ ID NOs:1, 3, 22, or 27] SEQ ID NO:1.

6. (Amended) A substantially pure polypeptide comprising the amino acid sequence of [any one of SEQ ID NOs:1, 3, 22, or 27] SEQ ID NO:1, with up to 30 conservative amino acid substitutions, wherein the polypeptide is a transporter of an organic cation.

7. (Amended) A substantially pure polypeptide encoded by a nucleic acid that hybridizes [under stringent conditions] to a probe the sequence of which consists of [any one of SEQ ID NOs:2, 4, 23, or 28] SEQ ID NO:2, under conditions of:

hybridization at 68°, followed by washing in 2 x SSC/0.1% SDS for 20 minutes at room temperature and twice in 0.1 X SSC/0.1% SDS for 20 minutes at 50°,

wherein the polypeptide is a transporter of an organic cation.